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(71) Applicants
Yamanouchi Pharmaceutical Co. Ltd.,
5-1 Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo, Japan
(72) Inventors
Hiroitsu Kawata
Masayoshi Aruga
Tadayoshi Ohmura
Takashi Sonobe
Satoru Yoneya
Chiharu Sone
(74) Agents
Reddie & Grose

(54) Sustained release pharmaceutical composition

(57) A sustained release pharmaceutical composition contains an amorphous solid medicament, and may also contain a polymeric additive e.g. polyethylene oxide, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, etc. The solid medicament, with or without additives, is obtained in amorphous form by drying a solution thereof e.g. by spray-drying, freeze-drying or drying in a fluidised bed granulator, to remove the solvent; or by comminuting the solid medicament with or without additives in a ball mill or in a vibrating ball mill. When the solid medicament is nicardipine, the composition may consist solely of the amorphous nicardipine or a salt thereof.

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SPECIFICATION

Sustained release pharmaceutical composition

The present invention relates to sustained release pharmaceutical compositions.

A sustained release pharmaceutical composition has many advantages such as reduced frequency of administration, decreases of side effects, and maintenance of effective concentrations of medicament in the blood. Accordingly, various types of sustained release pharmaceutical composition have hitherto been developed, for example, one containing a great amount of excipient which disintegrates slowly in the stomach or intestines, one in the form of a granule or tablet coated with repellent, one covered with semipermeable membrane, and one in which a polymer having low solubility or which is hydrophylic is mixed with, absorbed in or combined with a medicament to gradually release the medicament. As polymer for the latter purpose, there may be used acid-type carboxyvinyl polymer, polyvinyl alhocol, or polyacrylic acid, etc. However, sustained release pharmaceutical compositions usually give only relatively low bioavailability of active ingredient; and with a medicament of low solubility its effective concentration in the blood may not be obtainable or maintainable.

The present invention provides a sustained release pharmaceutical composition containing solid medicament in amorphous form. We have found that such compositions can exhibit satisfactory sustained release of the solid medicament.

The composition according to the invention may also contain polyethylene oxide (PEO), and preferably at least one additive (1) selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidone, carboxyvinyl polymer, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, methyl meta-acrylate meta-acrylic acid copolymer, polyvinylacetal diethylaminoacetate, dimethylaminoethyl meta-acrylate meta-acrylic acid copolymer, 2 - methyl - 5 - vinylpyridinemethyl acrylate meta-acrylic acid copolymer, citric acid, urea, succinic acid and amino acids; it may also contain at least one further additive (2) selected from surface active agents, polyethylene glycol, propylene glycol, glycerin, glycerin fatty acid esters and vegetable oils. PEO wherever mentioned herein can be replaced fully or partially by carboxypolymethylene (CPM) — e.g. "Carbopol".

We have also found that solid nicardipine (2,6 - dimethyl - 4 - (3' - nitrophenyl) - 1,4 - dihydropyridin - 3,5 - dicarboxylic acid - 3 - methyl ester 5 β - (N - benzyl - N - methylamino) - ethyl ester) or a salt thereof can be used alone in amorphous form to provide a sustained release pharmaceutical composition.

Accordingly, the invention also provides a substained release pharmaceutical composition of solid nicardipine or a salt thereof in amorphous form. This composition preferably contains PEO and/or CPM, and can, but need not, contain any of the above listed additives.

Some compositions of the invention can be obtained by a method in which the solid medicament and additive(s) from the above lists are dissolved in an organic solvent (e.g. one or more of methanol, ethanol, chloroform, dichloromethane) or water, and then the solvent is removed. The removal of the solvent can be carried out by drying under reduced or normal pressure, spray drying, fluidized-bed granulating drying, or lyophilization, etc. A fine powder or fine particle granules are thus obtained in which solid medicament is dissolved or dispersed uniformly in amorphous form in the additive(s). Then PEO and/or CPM is added and mixed in to provide the sustained release pharmaceutical composition.

Another method instead includes PEO and/or CPM in the solution, to become uniformly dissolved or dispersed with solid medicament in the additive(s) on solvent removal.

Any medicament, of low or high solubility, can be used in the invention to be retained in the gastroenteric tracts for long periods, examples being nicardipine hydrochloride, nifedipine, indenerol, indomethacin, buformin hydrochloride, etc.

Examples of suitable amino acid additives are threonine, glycin, alanin, cystein, lysin, etc. Suitable surface active agents include anionic agents such as sodium alkylsulfate, and non-ionic agents such as polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester, polyoxyethylene castor oil derivatives, etc. Exemplary vegetable oils are sesame oil, corn oil, soybean oil, rapeseed oil, olive oil, coconut oil, etc.

The compounding ratios of the components in the pharmaceutical composition vary according to the solid medicament used and its administration dose. Usually, it is appropriate to use 0.5-20 (preferably 1-10) parts by weight of additive(s) (1) and 0.05-10 (preferably 0.1-5) parts by weight of additive(s) (2), per part by weight of solid medicament. The compounding ratio of PEO and/or CPM is suitably 0.1-50 (preferably 0.5-30) parts by weight per part by weight of combined solid medicament plus said additives.

Preferred substained release pharmaceutical compositions according to the invention have PEO and/or CPM compounded in the fine powder or fine particle granules in which solid medicament is contained in amorphous form. Hitherto, polyethylen oxide has been used as a coating agent or binder in the preparation of pharmaceutical compositions, but it has not been reported that a sustained release pharmaceutical composition can be obtained by compounding polyethylene oxide with a solid medicament in amorphous form as in the present invention.

The pharmaceutical compositions of the present invention can be formulated as powders, granules, tablets, pills, or capsules in conventional manner. In the preparation of such formulations, there may be used conventional diluting agents, binders, viscosity-increasing agents etc. Further, according to the kind of solid medicament, a compound for dissolving the latter quickly can be included or treatm nt for dissolving th comp sition in the int stines

can be applied.

As mentioned above, th invention can provide in sustained release form the medicament nicardipine, which possesses coronary and cerebral vascular dilator activity and is useful for curing cerebral vascular disease, hypertension and angina pectoris. Hitherto, it has been difficult to provide a sustained release nicardipine composition because of its low solubility in the intestines. Nicardipine and its salts are easily dissolved in the first liquid (artificial gastric juice) of Japanese Pharmacopeia, thus exhibiting sufficient medical activity as usually formulated, but are only slightly soluble in the second liquid (artificial intestinal juice).

We have found that a sustained release nicardipine composition can be obtained by using amorphous nicardipine without adding substances to improve its solubility in the intestines. This composition can sustain an effective concentration of nicardipine in the blood for long periods due to good absorbability by the intestinal tract membrane, in spite of the low solubility of nicardipine in intestinal juice.

Amorphous nicardipine (and its salts) used in the present invention can be prepared by friction-pulverizing nicardipine powder, preferably using a ball mill or vibrating ball mill.

In the pulverizing step, it may be desirable to add one or more substances to decrease the adherence and massing of the nicardipine or nicardipine salt. Examples of such substances are calcium lactate, TC-5 (trade name, Shinetsu Kagaku Kogyo Co., ingredient: hydroxypropylmethyl cellulose), Avicel (trade name, Asahikasei Kogyo Co., ingredient: crystalline cellulose), etc. The change of nicardipine or its salt to the amorphous form in the pulverizing step can be confirmed by X-ray diffraction.

The amount of nicardipine or nicarpidine salt is usually 5-90% (preferably 10-70% and more preferably 20-40%) of the total weight of the composition. Nicardipine powder is usually in crystalline form; for example, nicradipine hydrochloride is a crystal having a melting point of 168-170°C. It is however possible to produce amorphous nicardipine by synthesis or purification, and in that case the amorphous nicardipine obtained can be used as it is for preparing a composition of the present invention.

The fine powder of amorphous nicardipine and its salts exhibits a sustained release effect when coated to avoid disintegration and dissolution in the stomach. It can also exhibit such effect with addition of pH-depending agent, viscosity-increasing agent or water-insoluble agent before or after pulverizing.

Examples of pH-depending agent are bases soluble in the intestines such as cellulose acetate phthalate, hydroxypropylmethyl cellylose, Eudragit L, S, RL and RS (trade names, Rome and Haas Co., ingredient acrylic acid meta-acrylic acid ester copolymer, or meta-acrylic acid m ta-acrylic acid ester copolymer), etc.; as viscosity-increasing agents there are polyethylene oxid , Carbopol (trade name, B. F. Goodrich Co., ingredient: carboxyvinyl polymer), sodium polyacrylate, sodium arginate, carboxymethyl cellulose calcium, carboxymethyl cellulos sodium, polyethylene glycol (molecular weight: 6000-20000), etc.; and as water-insoluble agents there are crystalline cellulose (for example, Avicel (trade name)), calcium phosphate, etc.

The degree of pulverizing of the nicardipine or its salt and the amount of the above agents added can be selected to predetermine when and over what period the medicament is released.

The present invention is illustrated by the following Experiment and Examples wherein, except for in the Control Experiment, the solid medicament used in each case is in amorphous form.

Experiment

Control:

After pulverizing the crystalline powder of nicardipine hydrochloride in a sample mill (using 1 mm screen), mini tablets each weighing 35 mg were prepared in conventional manner according to the following prescription. The tablets were coated with cellulose acetate phthalate the film of which is soluble in the intestines, to provide tablets soluble in the intestines.

Prescription	
Nicardipine hydrochloride	5.0 mg
Lactose	20.3 mg
Corn starch	7.0 mg
Hydroxypropyl cellulose	1.4 mg
Carboxymethyl cellulose calcium	1.1 mg
Magnesium stearate	0.2 mg
	35.0 mg

Pharmaceutical Composition of the present invention:

20 g of the crystalline powder of nicardipine hydrochloride, 4 g of TC-5 (trade name) and 38 g of Avicel (trade name) were pulverized for 16 hours in a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to amorphous form. Using the powder thus obtained, tablets each weighing 312 mg were prepared according to the following prescription and were coated with cellulose acetate phthalate to be dissolved in the intestines.

Prescription:	
Nicardipine hydrochloride	40 mg
TC-5	8 mg
Avicel	76 mg
Particles 209 for direct compression (Fiji Kagaku Kogyo Co.)	120 mg
Carboxymethyl cellulose calcium	64 mg
Magnesium strearate	4 mg
	312 mg

Conc ntration in blood when orally administered to dogs:

Sample	Number of dogs	Dose	Concentration in blood plasma (ng/Kg) 1hr	2hr	3hr	4hr	6hr	8hr	10hr	12hr	Area under the curve of conc. in blood plasma [(ng/Kg) · hr]
Control Phrm.Com.	6	5mg/Kg	7.7	6.9	3.4	1.3	0.1	9.2	–	–	29.35
of this invention	6	10mg/Kg	103.0	156.1	127.7	89.0	141.7	55.9	56.0	35.4	1062.90

Example 1

1000 g of a mixture of dichloromethane and methanol (1 : 1 in weight ratio) was added to a mixture of 50 g of nicardipine hydrochloride and 100 g of hydroxypropylmethyl cellulose to provide a solution. The organic solvent of the solution was distilled off by spray-drying to provide fine particle powder. To 50 g of the fine particle powder thus obtained were added 30 g of the fine particle powder of polyethylene oxide and 3.3 g of talc, and they were mixed uniformly. Capsules were prepared by filling each 250 mg of the mixture into No. 1 capsules.

Example 2

1000 g of dichloromethane was added to a mixture of 50 g of nifedipine, 50 g of polyethylene glycol 400 and 250 g of polyvinyl pyrrolidone to provide a solution, and 25 g of magnesium meta-silicate aluminate was dispersed uniformly in the solution. Using a fluidized-bed granulator, 350 g of anhydrous calcium hydrogen phosphate was fluidized and sprayed with the above solution to provide fine granules. To 250 g of the fine granules thus obtained were added 89.5 g of the fine particle powder of polyethylene oxide, 7 g of talc and 3.5 g of magnesium stearate, and they were mixed uniformly. Tablets each weighing 350 mg were prepared using an oblong punch having a major axis of 14 mm and a minor axis of 7 mm.

Example 3

3000 g of a mixture of dichloromethane and methanol (1 : 1 weight ratio) was added to a mixture of 100 g of indomethacin, 200 g of hydroxypropyl cellulose and 20 g of polyethylene oxide to provide a solution. The organic solvent of the solution was distilled off by spray-drying to provide fine particle powder. To 160 g of the fine particle powder thus obtained were added 80 g of polyethylene oxide and 10 g of talc, and they were mixed uniformly. Capsules were prepared by filling each 250 mg of the mixture into No. 1 capsules.

Example 4

400 g of methanol was added to a mixture of 20 g of nicardipine hydrochloride, 40 g of hydroxypropylmethyl cellulose phthalate and 10 g of polysorbate 80 to provide a solution. The organic solvent of the solution was distilled off by drying under r duced pressure to provide a solid material. The solid material was pulverized to fine particle powder. To 35 g of the fine particle powd r thus obtained were added 105 g of fine crystalline cellulose, 80 g of polyethylene oxide and 10 g of talc, and they were mixed uniformly. Capsules were prepared by filling each 230 mg of the mixture into No. 1 capsules.

Example 5

15 g of the crystalline powder of nicardipine hydrochloride, 3 g of TC-5 (trade name), 20.6 g of Avicel (trade name) and 18.2 g of HP-55 (trade name, Shinetsu Kagaku Kogyo Co., ingredient: hydroxypropylmethyl cellulose phthalate) were pulverized for 16 hours in a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to the amorphous form. Using the powder thus obtain d, the tablets each weighing 500 mg were prepared according to the following prescription.

Prescription:	
Nicardipine hydrochloride	75 mg
TC-5	15 mg
Avicel	103 mg
HP-55	91 mg
Particles 209 for direct compression	125 mg
Carboxymethyl cellulose calcium	20 mg
L-HPC (L-H31)*	66 mg
Magnesium stearate	5 mg
	500 mg

* L-HPC(L-H-31): Trade name, Shinetsu Kagaku Kogyo Co. ingredient: lower substituted hydroxypropyl cellulose

Example 6

20 g of the crystalline powder of nicardipine hydrochloride, 20 g of polyvinyl pyrrolidone K-30 (trade name, BASF Co.), HP-55 (trade name) and 4 g of Carbopol-940 (trade name) were pulverized for 16 hours in a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to amorphous form. Using the powder thus obtained, tablets each weighing 360 mg were prepared according to the following prescription.

Prescription:	
Nicardipine hydrochloride	60 mg
Polyvinyl pyrrolidone K-30	20 mg
HP-55	180 mg
Carbopol-940	12 mg
Polyethylene glycol 6000	48 mg
	360 mg

Example 7

40 g of the crystalline powder of nicardipine hydrochloride, 200 g of calcium lactate and 20 g of polyethylene oxide 18 w re pulverized for 10 hours in a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to amorphous form. Using a fluidized-bed granulator ("Uniglat" trade name, Okawara Seisakusho Co.), 195 g of the powder thus obtained and 150 g of Kalica GS (trade name, Kyowa Kagaku Kogyo Co., ingredient: anhydrous calcium hydrogen phosphate) wer fluid-

ized, sprayed with a solution of 20 g of polyethylene oxide-18 in 3000 ml of methylene chloride, and treated in conventional manner to provide fine granules. Capsules were prepared by filling each 365 mg of the fine granules thus obtained into No. 1 capsules in conventional manner.

Example 8

the crystalline powder of nicardipine hydrochloride, 80 g of Eudragit RL (trade name, Rohm and Hass Co., ingredient: acrylic acid meta-acrylic acid ester copolymer), 4 g of sodium arginate and 200 g of Avicel (trade name) were pulverized for 16 hours in a vibrating ball mill, whereby the crystals of nicardipin hydrochloride were changed to amorphous form. Using the powder thus obtained, tablets each weighing 600 mg were prepared according to the following prescription.

Prescription:

Nicardipine hydrochloride	60 mg
Eudragit RL	120 mg
Sodium arginate	6 mg
Avicel	300 mg
Lactose	78 mg
Corn starch	30 mg
Magnesium stearate	6 mg
	600 mg

Example 9

50 g of the crystalline powder of nicardipine hydrochloride and 250 g of TC-5 (trade name) were pulverized for 16 hours in a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to amorphous form. To 120 g of the powder thus obtained were added 140 g of lactose and 150 g of Avicel (trade name), and they were mixed uniformly. The mixed powder thus obtained was rotated in a coating pan used in usual sugar coating, and sprayed with a solution of 10 g of methyl cellulose in 1000 g of water to provide pills of 32-18 mesh. Half of the pills thus obtained were recovered, and the remaining half were further rotated in the same coating pan and sprayed with a solution of 10 g of Eudragit RL (trade name) in a mixture of 70 g of acetone and 130 g of isopropanol. Then all of the pills were combined and mixed uniformly. Capsules were prepared by filling each 450 mg of the mixture into No. 0 capsules.

CLAIMS

1. A sustained release pharmaceutical composition containing solid medicament in amorphous form.

2. A composition according to claim 1 in which the amorphous solid medicament comprises nicardipine or a salt thereof.

3. A composition according to claim 1 or 2 in which the medicament is compounded with polyethyl ne oxide and/or carboxypolymethylene.

4. A composition according to any prec ding claim including at least one additive selected from pH-depending agents, viscosity increasing agents, and water-insoluble agents.

5. A composition according to any preceding claim which contains at least one of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidon , carboxyvinyl polymer, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, methyl meta-acrylate meta-acrylic acid copolymer, polyvinylacetal diethylaminoacetate, dimethylaminoethyl meta-acrylate meta-acrylic acid copolymer, 2 - methyl - 5 - vinylpyridinmethyl acrylate meta-acrylic acid copolymer, citric acid, urea, succinic acid and amino acid.

6. A composition according to any preceding claim which also contains at least one of surface active agent, polyethylene glycol, propylene glycol, glycerin, glycerin fatty acid ester and vegetable oil.

7. A process of producing a sustained release pharmaceutical composition which comprises compounding a solid medicament in amorphous form.

8. A process according to claim 7 wherein the medicament is compounded with polyethylene oxide and/or carboxypolymethylene.

9. A process according to claim 8 which comprises dissolving in water or an organic solvent the solid medicament and at least one additive selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidone, carboxyvinyl polymer, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, methyl meta-acrylate meta-acrylic acid copolymer, polyvinylacetal diethylaminoacetate, dimethylaminoethyl meta-acrylate meta-acrylic acid copolymer, 2 - methyl - 5 - vinylprydidinmethyl acrylate meta-acrylic acid copolymer, citric acid, urea, succinic acid, amino acids, surface active agents, polyethylene glycol, propylene glycol, glycerin, glycerin fatty acid ester and vegetable oils, distilling off the solvent, and then adding polyethylene oxide and/or carboxypolymethylene.

10. A process according to claim 9 modified by dissolving the medicament, additive and polyethylene oxide and/or carboxypolymethylene in the solvent which is then removed.

11. A process according to claim 7 or 8 wherein the medicament is converted to amorphous form by pulverizing.

12. A process according to claim 11 wherein the medicament is pulverized in a ball mill or vibrating ball mill.

13. A process according to any of claims 7 to 12 wherein the medicament comprises nicardipine or a salt thereof.

14. A sustained release pharmaceutical composition substantially as hereinbefore described in any of the Examples.

15. A sustained release pharmaceutical composition according to claim 1 and substantially as hereinbefore described in the Experiment.

16. A process of producing a sustained release pharmaceutical composition, the process being substantially as hereinbefore described in any of the Examples.

17. A process of producing a sustained release pharmaceutical composition, the process being substantially as hereinbefore described in the Experiment.

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